Recommendations from Vaccine Clinical Trial Break out Group (March 2004 group A strep Vaccine Workshop)

1. Definition of clinical endpoints to evaluate in Phase III trials is needed to design a rational vaccine development plan and to determine the laboratory and epidemiologic data required to support vaccine development and implementation.

Two parallel tracks are recommended:

- In the U.S., where pharyngitis is responsible for high disease burden and considerable utilization of health care resources, protection against GAS pharyngitis should be the primary endpoint
- In developing countries, where rheumatic heart disease is the principal concern, the primary endpoint should be prevention of ARF

Secondary endpoints in both settings should include:

- Nested studies to characterize immune responses induced by vaccination These data are useful for bridging studies which establish comparability of vaccine responses among different populations. For example, the FDA might accept a claim that the vaccine prevents ARF if efficacy is shown in developing countries and the vaccine evokes similar immune responses in the U.S. population
- Nested studies to identify immune responses that correlate with clinical protection
- Cost effectiveness analysis

<u>Ancillary considerations:</u>

- Trials to support licensure in other industrialized countries should be considered to cultivate a broad market for a pharyngitis vaccine
- Ongoing dialogue with advisory agencies (AAP and ACIP) is needed to assist manufacturers in predicting vaccine uptake
- Epidemiologic studies should be conducted to identify subpopulations that would be amenable to a trial in which prevention of invasive disease is the primary endpoint
- Statistical modeling is needed to understand the feasibility of powering a study to detect the possibility that vaccination increases the risk of ARF
- After Phase I and II studies in healthy low risk adults have been completed, a trial should be considered to evaluate the safety of vaccination in subjects who had a previous episode of ARF. Efficacy of vaccination in preventing secondary ARF attacks should be evaluated if feasible.

2. A rational approach to the evaluation of GAS safety is needed, given the complex safety concerns related to GAS vaccines and the lack of validated tests to detect unwanted vaccine effects. The following paradigm was recommended:

   – Phase I studies should be performed in a subset of each age group in which the vaccine is evaluated. The aim of these studies is to perform a detailed, intensive evaluation of a small number of subjects who lack known risk factors for ARF (I.e., a personal or family history of ARF) and lack features that could be confused with an auto-immune diathesis (e.g., elevated CRP, C3 complement, cross-reactive antibodies). The evaluation should include:
     - Serial echocardiograms performed in a controlled fashion using the same reader, machine, and technician, and applying well-defined echocardiographic criteria for study inclusion and for changes from baseline
     - Serial measurements of cross reactive antibodies (coupled with T cell western blots if positive antibody responses are found); however, since the presence or absence of these antibodies has not been directly correlated with clinical disease, the protocol should stipulate how the results will be managed and should clearly state that isolated seroconversions are not absolute stopping criteria
     - Other safety evaluations should include EKG, urinalysis, CRP, and C3 complement

   – Phase II studies need not include the detailed echocardiogram, cross-reactive antibody, and other protocol-driven laboratory tests described for Phase I, but instead can rely on clinical history plus guided physical examination, with the caveat that evaluators are well-trained in cardiac ausculation

3. The optimal age of vaccination must be determined early in the development process. Assuming a 3-dose regimen will be required, this decision involves the following considerations:

   School age series
   - Pro: the group at highest risk for pharyngitis and ARF
   - Cons:
   - at this age, no routine 3-dose immunizations are given and physician contacts are at a nadir, although with some new vaccine candidates on the horizon, innovative strategies for vaccinating this age group may be needed
     - Toddlers experiencing pharyngitis and infants at highest risk for invasive disease would remain unprotected

   2-5 year old series
   - Pro: potential to prevent daycare associated GAS infections as well as pharyngitis and ARF in school aged children

- Cons: as above; must determine whether incidence of pharyngitis is high enough in this age group to conduct an efficacy trial
  - Infant series
    - Pros:
      - Potential to prevent disease in all age groups
      - Can be incorporated into routine vaccination schedule
    - Cons:
      - Must address possible antigenic interference with concomitant vaccines
      - Protection must endure for longer period to cover school age children
      - Efficacy trials must be continued over several years to detect case Clinical outcome age range